Remarks

Claims 56-66 are amended herein. Claims 56-64 are amended to indicate that the antibody is "purified" as requested in the Office action dated June 7, 2005. Support for this amendment can be found throughout the specification, for example at page 35, line 15 to page 39, line 32, such as on page 35, lines 23-24. Support for the additional amendment of claim 56 can be found throughout the specification, specifically at page 30, lines 19-21, page 35, lines 15-17, page 38, lines 4-6 and page 56, lines 32-34. Support for the additional amendment of claim 56 can also be found in the specification at page 35, line 15 to page 39, line 32, for example at page 36, lines 1-15. Claims 65 is amended to recite specifically limitations included in claim 56, from which it depends. Claim 66 is amended to include the limitations of claim 56.

New claim 67 is added herein. Support for new claim 67 can be found throughout the specification such as on at page 56, lines 33-34 and page 35, line 15 to page 39, line 32.

Applicants believe no new matter is added. Reconsideration of the subject application is respectfully requested.

Sequence Requirements

Submitted herewith is a replacement sequence listing in paper and electronic format, and a statement of compliance, as requested in the Notice to Comply with Requirements for Applications Containing Nucleotide and/or Amino Acid Sequences. A copy of the Notice to Comply is also enclosed, as requested in the Office action. Applicants note that the errors in the sequence listing were not delineated in the Office action. Applicants have made every effort to comply with the sequence requirements, and have checked the sequence listing with the U.S. PTO's Checker 4.0 program. If for any reason the attached paper and electronic copy are found not to be in compliance with 37 C.F.R. § 1.821-1.825, Applicants request that the U.S. PTO provide detailed comments on the deficiencies of the sequence listing.

Rejections 35 U.S.C. § 101

Claims 56, 63 and 64 are rejected as allegedly being related to non-statutory subject matter, as encompassing antibodies as they exist in nature. Claims 56 and 63-64 are amended herein to recite "an isolated antibody" as suggested in the office action on page 3. Applicants

submit that the amendment of the claims in accordance with the Examiner's helpful suggestion renders the objection moot.

Claims 56-66 are rejected under 35 U.S.C. § 101 as allegedly not supported by a substantial asserted utility or a well established utility. Applicants respectfully disagree with this assertion.

The Office action asserts that as the specification does not provide any objective evidence on the expression of Int6 protein in human tissues, and as the specification does not provide a specific teaching of the expression of Int6 protein in human or mammary epithelial cells, then the claimed antibodies cannot have any use. The Office action further asserts that as the specification only discloses the role of mouse Int6 in mammary cancer, then the specification simply cannot support a substantial utility for either the human polypeptide, the regulation of epithelial cell growth, or the whether binding would be to a specific diseased tissue. Applicants respectfully disagree with this rejection.

The specification clearly discloses that the loss of expression of full-length Int6 is associated with human breast and lung cancer (see for example, page 55, line 15 to page 56, line 22). Submitted herewith is the Summary for Protein A003493, Int6, published February 8, 2005 (copy attached as Exhibit A), which describes that breast tumor formation is associated with truncated Int6 proteins. Similarly, the ability of truncated Int6 protein to cause the transformation of human mammary epithelial cells is documented in Rasmussen et al., Oncogene 20: 5291-5301, 2001 (copy attached Exhibit B). Yin and Chang (Cell Cycle 2: 81-83, 2003) also describe the function of Int6 proteins, disclose that truncation of Int6 results in transformation, and describe that the "loss of Int6 functions can have a profound effect on breast tumorigenesis." All of these documents, published after the filing date of the parent application, document that the loss of expression of full length Int6 is associated with cancer.

The specification also discloses that the claimed antibodies can be used in ELSIA assays, Western blot assay, and radioimmune assays for the Int6 protein (for example, see page 39, lines 11-20). Applicants would like to take this opportunity to remind the Examiner that the present application is a divisional patent application. Parent U.S. Patent Application No. 09/378,842, which issued as U.S. Patent No. 6,342,392, includes claims directed to methods of assaying a sample to detect the presence Int6, comprising contacting the sample with antibody directed

against Int6 protein or peptide fragments thereof. Thus the U.S. PTO has previously determined that that methods for assaying the presence of Int6 (that include the use of antibodies that specifically bind Int6), have a credible, specific and substantial utility. Applicants submit that if assays for Int6 proteins that utilize antibodies have a credible, specific and substantial utility then the antibodies themselves must also have a credible, specific and substantial utility.

In addition, more than one utility is disclosed for isolated antibodies that specifically bind Int6. The specification discloses that the claimed antibodies are of use in a purification process (see page 38, lines 30-32) for Int6 protein. The specification also discloses that the claimed antibodies can be used in immunohistochemical localization of the Int6 protein (see page 39, line 14-32). Thus, more than one clear, specific and credible use is established by the specification.

The Office action (see page 6) further asserts that the specification fails to provide guidance as to how one of skill in the art could use the claimed invention in a way to provide a substantial utility. Applicants respectfully disagree with this assertion. The specification specifically describes assays to detect alterations of the expression of Int6 protein in detail (see for example, page 39, lines 1 to 32), and discloses that this assay is of use with specimens such as tumor biopsies, including but not limited to breast tumor biopsies. Thus, the specification clearly provides detailed guidance as to how the claimed antibodies can be utilized.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 62 was rejected for including the limitation "the kit of claim 62." Applicants were not able to identify this phrase in claim 62. Applicants believe that the rejection was intended to be asserted against claim 66. Claim 66 is amended herein to depend from claim 62, and to incorporate that limitations of claim 56. Applicants believe that these amendments render the rejection moot.

Claim 56 is rejected as allegedly being indefinite for the recitation of "deregulates mammary epithelial cell growth," as allegedly "the exact meaning of the words are not known." The Office action states that "the primary deficiency in the use of this phrase is the absence of an ascertainable meaning for said phrase."

Applicants respectfully disagree with this rejection, and submit that the U.S. PTO has determined previously that the phrase is clear and definite. In addition, fragments of Int6 that

deregulate mammary cell growth are fully described in the specification; the specification clearly describes the de-regulation of mammary epithelial growth, for example on page 50, line 27 to page 51, line 2. It is disclosed in the specification that a de-regulation of mammary epithelial cell growth leads to hyperplasia of mammary cells; polypeptides comprising amino acids 60-108 or amino acids 235-268 of Int6 that deregulate mammary epithelial cell growth are disclosed (see, for example, page 8, lines 1-14 and Fig. 9). Rasmussen et al., Oncogene 20: 5291-5301, 2001 (Exhibit A) further demonstrates that a truncated Int6 protein is "sufficient to transform the growth properties of both mammary epithelial cells and NIH3T3 cells;" see for example page 5296, second column of this publication. Thus, Applicants submit that one of skill in the art readily understands the phrase "de-regulation of epithelial cell growth" and that the term is clear and definite.

However, solely to advance prosecution, claim 56 has been amended to recite that the fragment is about 20 to 24 consecutive amino acids of SEQ ID NO: 4. Applicants submit that the amendment of claim 56 renders the rejection moot.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 56-66 are rejected as allegedly not being enabled by the specification. The Office action states that although the expression Int-6 mRNA is disclosed to be lost in human tumors, there is no specific teaching of the loss of expression of the protein itself in human tumors. The Office action asserts that an increased copy number of DNA or the presence of an mRNA does not support a use for a polypeptide unless there is information on the level of expression and its role of the protein. Cited in support of this assertion is Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465).

Alberts et al. teach that the stability of an mRNA can be changed in response to extracellular signals. In the absence of iron, the translation of ferritin mRNA is blocked, so that no protein is produced. Thus, an mRNA can be present, but the protein can or cannot be translated. The Office action cites a number of references indicating that the presence of an mRNA does not necessarily indicate that the mRNA is translated into protein.

However, the cited prior art only teaches that the presence of a full length mRNA need not necessarily result in the production of a full-length polypeptide. *This is a distinct and different situation than what is shown in the specification.* The specification teaches that it is the

loss of full-length Int6 mRNA that correlates with human breast cancer and lung cancer (for example, page 56, lines 14-22). It logically follows that in the absence of full-length Int6 mRNA, the production of full-length protein cannot occur (as there is no full-length mRNA to translate). Thus, the amount of full-length Int6 protein must be decreased in the breast cancer and lung cancer cells (as there is no full-length mRNA that can be translated into full length protein).

In one example, the specification also provides an analysis of genomic DNA in human breast tumor DNA. The results demonstrated that there was a loss of heterozygosity; there was a complete loss or a significantly reduced signal of one allele (DNA). In the absence of Int6 allele (DNA), Int6 mRNA is not transcribed from the deleted DNA. Again, in the absence of Int6 mRNA, full-length Int6 protein simply could not be produced from the Int6 allele.

In addition, Applicants submit that the role of Int6 protein in transformation and tumorigenesis has been supported by further work. Post-filing date evidence (see Exhibits A-C, described above) documents that antibodies that specifically bind SEQ ID NO: 4 can be produced and utilized to detect Int6 protein. The additional work, published after the filing date of the present application, provides confirmatory evidence that breast tumor formation is associated with *truncated* Int6 proteins, as stated in the specification.

However, Applicants believe that this correlation (fully supported by the specification and post-filing date evidence) is not required for the enablement of claims 56-66. Applicants remind the Examiner that the pending claims are directed to antibodies that specifically bind SEQ ID NO: 4, or a fragment thereof.

Submitted herewith is a printout of the presentation made by Bonnie Eyler, Quality Assurance Specialist for Technology Center 1600 of the U.S. PTO (attached as Exhibit D for the convenience of the Examiner). This presentation was made at the Biotechnology and Chemical Pharmaceutical Customer Partnership Meeting on December 8, 2004. With regard to 35 USC 112, first paragraph, the statement that is made that "based on past precedent, as long as an applicant has disclosed a fully characterized antigen, either by its structure, formula, chemical name or physical properties, the applicant can then claim an antibody by its binding affinity." Reference is provided in this presentation to In re Noelle, 355 F.3d 1349 (Fed Cir. 2004). While Applicants note that Ms. Eyler provides discussion with regard to written description, Applicants submit that the precedent established by the Court clearly also applies to enablement.

Moreover, Applicants note that Ms. Eyler discuss all of the issues for examination of claims directed to antibodies that specifically bind an antigen of interest. Ms. Eyler describes issues with regard to Written Description and rejections based on the prior art for claims directed to an antibody that binds a protein of a known amino acid sequence . However, Ms. Eyler does not draw any distinction with regard to enablement of claims to antibodies that specifically bind a characterized protein.

Claim 56 is in the format discussed in Ms. Eyler's presentation, namely an isolated antibody or fragment thereof which specifically binds a specified sequence. The Applicants have provided a fully characterized antigen, including its amino acid sequence (SEQ ID NO: 4) and the sequence of proteins that are functional fragments (proteins comprising amino acids 60-108 of SEQ ID NO: 4 and proteins comprising amino acids 235-268 of SEQ ID NO: 4, as noted at page 7, line 16 to page 8, line 14 and Fig. 9). Moreover, a cDNA encoding SEQ ID NO: 4 has been a deposited in accordance with the Budapest Treaty (Int6 cDNAs are deposited as ATCC Accession No. 97209 or as ATCC Accession No. 97030). Thus, as suggested in slides 8-10 of Ms. Eyler's presentation, the Applicants are entitled to claim an antibody by its binding affinity to SEQ ID NO: 4 or functional fragments thereof. Applicants submit that the claimed antibodies are fully enabled by the specification.

Reconsideration and withdrawal of the rejection is respectfully requested.

Prior Art and

The Information Disclosure Statement Previously Submitted to the US PTO

Applicants note that the Office action did not assert any rejections based on the prior art. Thus, it is the Applicants understanding that claims 56-66 were found to be free of the prior art of record. Applicants note that an Information Disclosure Statement (IDS) was submitted on February 19, 2004. However, a signed copy of the PTO-1449 that accompanied the IDS was not provided with the Office action. Applicants respectfully request that the Examiner return the initialed copy of the PTO-1449 to formally indicate that the prior art has been made of record, and to indicate that the prior art cited therein has been considered by the Examiner.

Conclusion and Request for an Interview

Applicants thank Examiner Davis for the courtesy telephone call confirming that this application has been transferred to her docket. As discussed with Examiner Davis, if any matters remain to be addressed before a Notice of Allowance is issued, the Applicants respectfully request that Examiner Davis contact their undersigned representative for a telephone conference.

Respectfully submitted,

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